Oxygen sensing, potassium channels, and the ductus arteriosus.

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The ductus arteriosus (DA) plays a critical role in normal and abnormal cardiovascular physiology of the fetus and newborn (1). In utero, patency of the DA allows blood to flow from right ventricle to aorta, enhancing placental blood flow, and promoting fetal oxygenation and well-being. The DA constricts within hours after birth and later undergoes permanent closure through structural remodeling due to smooth muscle cell migration into the constricted vascular lumen, formation of intimal cushions, and marked fibrosis. That patency of the DA is essential in utero has been demonstrated clearly by observations that premature DA closure causes pulmonary hypertension, congestive heart failure, hypoxemia, and hydrops fetalis. In contrast, failure of postnatal ductal closure contributes to pulmonary edema and other complications in the premature neonate with severe respiratory distress syndrome (RDS) or, later in infancy, the need for surgical intervention to avoid development of pulmonary hypertension (1, 2). Based on extensive studies from the laboratories of Rudolph, Heymann, Friedman, Olley, Coccaeni, and others, insights into mechanisms which regulate tone of the DA have led to successful pharmacologic manipulation of the DA to either sustain patency with PGE\textsubscript{2} infusions in ductus-dependent cardiac lesions or to promote closure with indomethacin in premature neonates with RDS (3–5). Despite these successes, however, some patients fail to respond to pharmacologic intervention, suggesting a continuing need for developing new clinical approaches.

Thus, insights into mechanisms which regulate DA tone and structural remodeling have implications for improving the clinical course of children with RDS, cyanotic congenital heart disease, pulmonary hypertension, and other problems. These mechanisms are also of interest to clinicians and scientists other than neonatologists and pediatric cardiologists, because lessons learned from studies of the DA are relevant to basic mechanisms in vascular biology, especially those regarding O\textsubscript{2} sensing and how changes in O\textsubscript{2} tension are transduced into specific cellular responses (6). As first observed over 50 yr ago, increased O\textsubscript{2} at birth causes DA constriction, while in marked contrast, smooth muscle from the fetal pulmonary circulation undergoes vasodilation. Insight into the unique responses of the DA to increased O\textsubscript{2} may provide valuable lessons into normal and pathologic vascular responses from other circulations and O\textsubscript{2} sensing in other biologic systems.

In this issue, Tristani-Firouzi and colleagues examine mechanisms by which increased O\textsubscript{2} constricts the fetal DA (7). Based on previous studies of the pulmonary circulation (8) and carotid body and neurons (9, 10), these authors hypothesized that K\textsuperscript{+} channels play a central role in mediating O\textsubscript{2}-induced DA constriction. The effects of O\textsubscript{2} and K\textsuperscript{+} and Ca\textsuperscript{2+} channel antagonists on DA tissue from fetal rabbits were studied in a thorough series of experiments, which included measurements of DA tone, intracellular Ca\textsuperscript{2+} content, whole-cell patch clamp studies, and cell attached single channel recordings. They report that increased O\textsubscript{2} inhibits a SbP\textsubscript{4}, delayed rectifier (K\textsubscript{DR}) K\textsuperscript{+} channel in DA smooth muscle cells, causing membrane depolarization, increased Ca\textsuperscript{2+} entry via activation of L-type Ca\textsuperscript{2+} channels, and DA constriction. Inhibition of ATP-sensitive or Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels had little effect, suggesting that the response to O\textsubscript{2} was primarily due to inhibition of K\textsubscript{OR} channels and activation of L-type Ca\textsuperscript{2+} channels.

These findings demonstrate important mechanisms underlying the unique responses of the DA to changes in O\textsubscript{2}. O\textsubscript{2}-sensitive K\textsuperscript{+} channels were first described in carotid body chemoreceptors (9), and subsequently have been shown to regulate vascular tone in pulmonary and systemic (coronary, cerebral) circulations. In the fetal lung, low O\textsubscript{2} may inhibit Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels, causing membrane depolarization, activation of voltage operated calcium channels, and vasocostriction (11). In the adult pulmonary artery, hypoxia inhibits a K\textsubscript{OR} channel and initiates vasoconstriction (8). In this study, hypoxia activates K\textsubscript{OR} channels in fetal DA smooth muscle, causing vasodilation, suggesting that changes in O\textsubscript{2} tension may cause subtypes of the same class of K\textsuperscript{+} channels to respond differently in DA or pulmonary artery smooth muscle. Since the K\textsubscript{OR} antagonist, 4-aminopyridine, constricts both the DA and pulmonary arteries, it appears that the K\textsubscript{OR} channel itself may not be the O\textsubscript{2} sensor, but involves an alternative mechanism. Further studies characterizing such differences are needed, including molecular approaches to define differences between sites and potential changes with ontogeny.

This study lacks in vivo demonstration of the role of K\textsuperscript{+} channels, and questions remain regarding how to integrate these observations with findings of other mechanisms involved with DA regulation. Past studies have clearly demonstrated the potent effects of PGE\textsubscript{2} and cyclooxygenase blockade on DA tone (1, 3, 4). Extensive studies from Coccaeni’s laboratory have more recently suggested that other vasoactive systems are involved with regulation of DA tone, including endothelin, carbon monoxide, nitric oxide, and the cytochrome P450 system (12, 13). How changes in O\textsubscript{2} tension and regulation of K\textsuperscript{+} channel activity interact with these systems is uncertain. In addition, although some of these systems appear operative in vitro, their effects on DA tone in vivo can differ (5, 14). For example, inhibition of NO synthase appears to have little effect on DA tone in vivo, despite apparent modulation of tone in vitro (14). In vivo, hemodynamic forces, including flow, shear stress, stretch, and pressure, may further modulate responses to changes in O\textsubscript{2} or vasoactive products. Further studies are needed to examine the relative roles of these vasoactive products in modulating DA tone, interactions between systems, the potential influence of circulating substances on DA tone, and other factors.

Thus, these novel observations provide new insights into the role of K\textsuperscript{+} channels in O\textsubscript{2}-induced constriction of the DA. Future studies examining similarities and differences in mechanisms between blood vessels from the pulmonary, cerebral, and other circulations may help clarify mechanisms of oxygen sensing and signal transduction, and are likely to have implications regarding vasoregulation. Once again, lessons learned
from the fetus and responses to postnatal adaptation may have much to teach us about basic biology.

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References